Spurious Hypocalcemia After Gadodiamide-Enhanced Magnetic Resonance Imaging: A Case Report and Review of the Literature

Christopher D. Moore, MD,* Robert C. Newman, MD,* James G. Caridi, MD†

Departments of *Urology and †Radiology, University of Florida College of Medicine, Gainesville, FL

Gadolinium-enhanced magnetic resonance imaging is a diagnostic modality widely used in urologic practice. We report on a 54-year-old woman in whom a critically low serum calcium level was measured with standard colorimetric assay after gadodiamide-enhanced magnetic resonance imaging. The same phenomenon was noted in 2 other patients seen in our practice. Repeat serum calcium measurements performed several hours later were within normal limits. Commercially available gadolinium-based contrast agents might precipitate critically low serum calcium values when measured by standard colorimetric assay. Physician awareness of gadodiamide-induced spurious hypocalcemia might prevent unnecessary therapeutic interventions.
[Rev Urol. *2006;8(3):165-168*]

Key words: Gadolinium • Magnetic resonance imaging • Hypocalcemia

Magnetic resonance imaging (MRI) has gained widespread use in urologic practice for diagnosis of various disease entities. The adjunct use of gadolinium provides specific information regarding tissue enhancement and blood flow, with fewer nephrotoxic effects when compared with conventional contrast material.[1] As a free metal, gadolinium is toxic, but the addition of chelates has facilitated its safe use.[2] When administered intravenously, gadolinium chelates are safely excreted, are not associated with nephrotoxicity, and show an extremely low incidence of allergic reactions.[2,3] Chelates currently in use are gadopentetate dimeglumine (Magnevist®; Berlex, Wayne, NJ), gadoteridol

(ProHance®; Bracco-Byk Gulden, Konstanz, Germany), gadodiamide (Omniscan®; GE Healthcare, Chalfont St. Giles, United Kingdom), and gadoversetamide (OptiMARK®; Tyco Healthcare, Mansfield, MA).[4] Interference of 2 of these agents, gadodiamide and gadoversetamide, with laboratory assays for serum calcium measurements has been reported in the literature. We report spurious hypocalcemia in 3 patients measured by automatic colorimetric testing after gadodiamide-enhanced MRI.

Patients

An asymptomatic 54-year-old woman was seen in our outpatient urology clinic for surveillance of a hemorrhagic renal cyst. Shortly thereafter, she underwent gadodiamide-enhanced (0.1 mmol/kg, intravenous injection) MRI of the abdomen and pelvis, followed immediately by phlebotomy for a metabolic panel. The patient was called back urgently the following morning when laboratory results revealed a serum calcium level of 2.6 mg/dL (reference range, 8.0–10.6 mg/dL), as measured by the colorimetric method using orthocresolphthalein (Roche Diagnostics, Indianapolis, IN).

The patient had chronic renal insufficiency, with a stable serum creatinine level of 1.4 mg/dL, and creatinine clearance of 55 mL/min. She also had a history of medullary sponge kidney and small bilateral renal calculi. There was no previous history of hypocalcemia. A repeat serum calcium measurement (18 hours after gadolinium administration) using the same protocol showed a level of 7.1 mg/dL.

The following week, a 34-year-old man with a baseline creatinine level of 1.3 mg/dL had a serum calcium measurement of 3.7 mg/dL 1 hour after gadodiamide-enhanced MRI of the abdomen and pelvis for surveillance of renal cell carcinoma after radical nephrectomy. A 63-year-old man with normal renal function was found to have a serum calcium level of 4.7 mg/dL 1 hour after gadodiamide-enhanced MRI of the abdomen and pelvis performed as surveillance for renal cell carcinoma after partial nephrectomy. Neither patient had a history of hypocalcemia. Both were called urgently for repeat laboratory testing, and in both cases repeat calcium levels were normal according to colorimetric assay approximately 18 hours after gadolinium administration.

The patient was called back urgently the following morning when laboratory results revealed a serum calcium level of 2.6 mg/dL (reference range, 8.0–10.6 mg/dL).

After the third occurrence, it became evident that the sample was obtained for serum calcium measurement immediately after imaging. None of the patients exhibited signs or symptoms of hypocalcemia.

Comment

In vivo and in vitro studies have documented the interference with colorimetric assays of 2 widely used gadolinium-based contrast agents, gadodiamide and gadoversetamide, resulting in spurious hypocalcemia. Other agents—gadopentetate dimeglumine, gadoterate meglumine (Dotarem®; Laboratoire Guerbet, Roissy, France), and gadoteridol—have not been shown to cause this interference.[5,6]

An earlier report in the literature by Normann and colleagues[7] documented the interference of gadodiamide with colorimetric determinations of serum calcium in a dose-dependent manner. Lin and colleagues[6] confirmed these findings and reported that the same interference was not seen with intravenous administration of gadopentetate dimeglumine. Later, Prince and associates[8] evaluated the prevalence of spurious hypocalcemia after gadodiamide-enhanced MRI by evaluating patients with available serum calcium levels before and immediately after gadodiamide-enhanced MRI. Correlations were determined with gadodiamide dose, renal function, and time between gadodiamide administration and phlebotomy. After 42 gadodiamide-enhanced examinations, serum calcium measurements spuriously decreased in 25 examinations. Spurious reductions in calcium measurements were greater in patients with renal insufficiency than in those with normal renal function. In addition, patients with renal insufficiency had spuriously low calcium measurements up to 4½ days after gadodiamide administration. Seven patients were inappropriately treated, and no patient had symptoms of hypocalcemia. The investigators concluded that gadodiamide-related hypocalcemia is more prevalent in patients who receive a dose of at least 0.2 mmol/kg (more commonly used with MR angiography) and in patients with renal insufficiency. A larger follow-up study by the same group confirmed these

After 42 gadodiamide-enhanced examinations, serum calcium measurements spuriously decreased in 25 examinations.

findings.[5] Finally, Williams and colleagues[9] reported a critically low calcium level as measured by standard colorimetric assay after intravenous administration of gadodiamide. A diagnosis of spurious hypocalcemia was made after immediate reanalysis of the same specimen using absorption spectroscopy.

In patients with normal renal function, a standard dose of gadodiamide (0.1 mmol/kg) has little effect on colorimetric calcium measurements, owing to its rapid excretion by the kidney.[10] The elimination half-life of gadodiamide, however, is prolonged in patients with pre-existing renal insufficiency and might result in durations of interference in the assay of more than 24 hours. In addition, doses of gadodiamide used in MR angiography are typically greater ($>$ 0.2 mmol/kg) than in standard MRI. A larger intravenous load in this circumstance, coupled with a patient population predisposed to atherosclerotic disease and/or renal insufficiency, is likely to amplify interference with calcium determinations for longer periods.[8]

Severe hypocalcemia is associated with neuromuscular irritability, tetany, laryngospasm, prolongation of the QT interval, arrhythmias, coma, and even death. Initial resuscitation for symptomatic patients consists of intravenous calcium administration. The mechanism of gadolinium-related spurious hypocalcemia is based on interference with the colorimetric assay caused by the chelate. In the arsenazo III dye and orthocresolphthalein colorimetric assays, standard to most laboratories in the United States, a colorimetric reagent that binds to calcium is added to the serum specimen. The result is a color change of the sample, which is then measured photometrically. The reagent, however, also binds to certain gadolinium-based agents and removes gadolinium from the gadodiamide chelate. The free chelate is then available to bind to serum calcium, causing a spuriously low result.[6–8,10] Because this reaction occurs exclusively in the laboratory sample, the patient's actual serum calcium level is not affected. Ionized, or free, calcium levels are not routinely measured unless specifically ordered by the requesting physician.

This interference of gadolinium-based contrast agents with serum calcium determinations is not widely known among practitioners and is not widely reported in the urologic literature. There are several implications for a delay in recognizing this phenomenon, including unnecessary resuscitative measures and treatment of a false laboratory value. Spurious results also lead to additional patient examinations and a possible delay in the diagnosis and management of underlying hypercalcemia.[8] Economic repercussions, including additional costs of laboratory handling of critical values, as well as the potential for liability for unnecessary treatment of a spurious value, must also be considered. When a critically low serum calcium level is encountered in practice, re-evaluation of the same sample with absorption spectroscopy or immediate examination of the patient for signs of true hypocalcemia have been suggested.[8]

Conclusion

Two gadolinium-based contrast agents commonly used in MRI, gadodiamide and gadoversetamide, might interfere with the colorimetric determination of serum calcium levels. The resulting spurious hypocalcemia might result in unnecessary resuscitation maneuvers. Patients with pre-existing renal insufficiency or those receiving higher doses of these contrast agents are at an especially high risk of spurious hypocalcemia. Two other gadolinium-based contrast agents, gadoteridol and gadopentetate dimeglumine, have not been to shown to interfere with serum calcium measurements. Recognition of the potential for spurious calcium measurements

Main Points

- Two gadolinium-based contrast agents commonly used in magnetic resonance imaging, gadodiamide and gadoversetamide, might interfere with the colorimetric determination of serum calcium levels, and the resulting spurious hypocalcemia might result in unnecessary resuscitation maneuvers.
- Patients with pre-existing renal insufficiency or those receiving higher doses of these contrast agents are at an especially high risk of spurious hypocalcemia.
- Two other gadolinium-based contrast agents, gadoteridol and gadopentetate dimeglumine, have not been shown to interfere with serum calcium measurements.
- Spurious values can be confirmed by repeat laboratory processing of a separate specimen, absorption spectroscopy examination of the same specimen, and examination of the patient for signs or symptoms of true hypocalcemia.

is necessary to prevent serious consequences of unnecessary treatment of spurious hypocalcemia. Spurious values can be confirmed by repeat laboratory processing of a separate specimen, absorption spectroscopy examination of the same specimen, and examination of the patient for signs or symptoms of true hypocalcemia. Clinicians should, therefore, be familiar with the particular gadolinium-based contrast agent used at their institution, as well as the laboratory assay used. ■

References

1. Tombach B, Bremer C, Reimer P, et al. Renal tolerance of a neutral gadolinium chelate (gadobutrol) in patients with chronic renal failure: results of a randomized study. *Radiology*. 2001;218:651-657.
2. Runge VM. Safety of magnetic resonance contrast media. *Top Magn Reson Imaging*. 2001;12:309–314.
3. Prince MR, Arnoldus C, Frisoli JF. Nephrotoxicity of high-dose gadolinium compared to iodinated contrast. *J Magn Reson Imaging*. 1996;6:162-166.
4. Muroff LR. MRI contrast: current agents and issues. *Appl Radiol*. 2001;30 (suppl):5-7.
5. Prince MR. More on pseudohypocalcemia and gadolinium-enhanced MRI. *N Engl J Med*. 2004; 350:87-88.
6. Lin J, Idee JM, Port M, et al. Interference of magnetic resonance imaging contrast agents with the serum calcium measurement technique using colorimetric reagents. *J Pharm Biomed Anal*. 1999;21:931-943.
7. Normann PT, Frøysa A, Svaland M. Interference of gadodiamide injection (OMNISCAN®) on the colorimetric determination of serum calcium. *Scand J Clin Lab Invest*. 1995;55:421-426.
8. Prince MR, Erel HE, Lent RW, et al. Gadodiamide administration causes spurious hypocalcemia. *Radiology*. 2003;227:639-646.
9. Williams SF, Meek SE, Moraghan TJ. Spurious hypocalcemia after gadodiamide administration. *Mayo Clin Proc*. 2005;80:1655-1657.
10. Emerson J, Kost G. Spurious hypocalcemia after Omnisan- or OptiMARK-enhanced magnetic resonance imaging. *Arch Pathol Lab Med*. 2004; 128:1151-1156.